

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
14 July 2005 (14.07.2005)

PCT

(10) International Publication Number
WO 2005/063236 A1

- (51) International Patent Classification⁷: A61K 31/381 (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (21) International Application Number: PCT/EP2004/014626
- (22) International Filing Date: 22 December 2004 (22.12.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 03029680.0 23 December 2003 (23.12.2003) EP
- (71) Applicant (for all designated States except US): SCHWARZ PHARMA AG [DE/DE]; Alfred-Nobel-Strasse 10, 40789 Monheim (DE).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): KRÄMER, Robert [DE/DE]; Archimedes Strasse 36, 51065 Köln (DE).
- (74) Agents: HOFFMANN EITLE et al.; Arabellastrasse 4, 81925 München (DE).
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/063236 A1

(54) Title: INTRANASAL FORMULATION OF ROTIGOTINE

(57) Abstract: This invention pertains to a liquid intranasal pharmaceutical formulation comprising a pharmaceutically acceptable acid addition salt of rotigotine and α -cyclodextrin, preferably in the form of a buffered aqueous solution having a viscosity of 0.5 - 1.5 mm²/s

Intranasal Formulation of Rotigotine

Description

5 Field of the Invention

The present invention relates to an intranasal pharmaceutical formulation containing a pharmaceutically acceptable salt of rotigotine. Such intranasal formulations are useful in the
10 treatment of diseases where the administration of rotigotine is beneficial, in particular in the treatment of morbus Parkinson and other dopamine-related disorders.

Background of the Invention

15

It is known that dopamine D2 agonists such as apomorphine or rotigotine may in principle be used to treat morbus Parkinson and other diseases for which an increase of the dopamine level is beneficial such as the restless leg syndrome (RLS).
20 However, due to the very high first-pass effect of most of these dopamine agonists and the problem that many Parkinson patients develop some kind of drug tolerance against these drugs, the development of a safe and effective pharmaceutical formulation by which controlled amounts of drug can be
25 administered is far from trivial.

Rotigotine (5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol, sometimes also designated as N-0923) and its pharmaceutically acceptable salts have been
30 previously administered to patients mainly in the form of transdermal delivery systems (see e.g. WO 94/07468, WO 99/49852, EP-A-1 256 339). However, there was also at least one attempt of an intranasal administration of this drug (Swart et al., Pharmaceutical Sciences 1995, 1: 437-440).
35 Swart et al. administered a solution of rotigotine hydrochloride in a 1:1 mixture of polyethylenglycol (PEG) 400 and water to male Albino Wistar rats. While they observed an improved bioavailability of rotigotine after buccal, nasal or

rectal administration compared with oral dosing in the rat, they also observed that the bioavailability for the nasal dosing was "somewhat disappointing" when compared with the results described for other lipophilic drugs. Swart et al. suggested that the relatively low bioavailability they observed may be explained by a low absorption or rapid metabolic conversion of the drug in the nasal mucosa. These authors further stated that as of 1995 no information was available about the influence of rotigotine on the ciliary function of the nasal mucosa. In their view, nasal medication may change or even destroy the epithelial cells, with the recovery taking a few hours to a few months depending on the agent (Van Donk et al., Rhinology 18: 93-104).

In view of this rather discouraging report, it is perhaps not very surprising that the nasal administration of rotigotine does not seem to have been further attempted in the years after 1995 until the present invention was made. The state of information on the influence of rotigotine on the ciliary function of the nasal mucosa remained basically unchanged since these days.

US-A-2003-0,124,191 discloses a pharmaceutical composition in powder form that is intended for administration through the mucosa. A large variety of active ingredients including, among many others, rotigotine may be used as the active principle of this formulation which may further contain wetting agents, binding agents, diluents, penetration enhancers and other ingredients. The penetration enhancers of this reference include, among many others, cyclodextrins. The administration routes described in this application are again multifold and comprise administration through the buccal mucosa, the nasal mucosa, the vaginal mucosa and sublingual administration. However, this reference does not specifically disclose an intranasal formulation of rotigotine and provides no teaching as to requirements and the necessary/suitable ingredients of such an intranasal formulation.

Apomorphine is a drug that shares certain functional features with rotigotine but is structurally different. Like rotigotine, apomorphine is a dopamine agonist and has therefore been used to treat various dopamine-related disorders, including morbus Parkinson. The nasal administration of apomorphine has also been tried. For example, WO 94/22445 describes pharmaceutical compositions for intranasal administration of apomorphine, morphine and dihydroergotamine. These drugs can be used in combination with saccharides or higher sugar alcohols.

J. Duarte et al. describe aspects of intranasal apomorphine in Parkinson's Disease in J. Pharmacol. Technol. 11:226-228 (1995). This report states on the one hand that intranasal administration of apomorphine is a comfortable and effective alternative to subcutaneous administration but on the other hand also mentions that one patient developed a nasal vestibulitis ("troublesome rhinitis") during chemical trials. While this patient could continue apomorphine therapy, doubts do remain of the general suitability of this therapy form when account is taken of the fact that only four patients participated in this study. A very similar report on such side effects is given in Ned Tijdschr Geneesk 1992; 136, nr 14, p.702. The authors of this reference suspect that apomorphine may bind as a hapten to proteins in the nasal mucosa and thus evoke an allergic reaction. Thus, even in the case of apomorphine, the problem of finding a safe (non-allergenic) and effective intranasal medication cannot be considered as having been solved satisfactorily.

More recently, the same findings with liquid intranasal formulations of apomorphine were confirmed again by Djupesland et al. in PFO Magazine, June/July 2002. These authors stated that while administration of liquid intranasal apomorphine has been shown to be effective in Parkinson's Disease, local side effects in the form of nasal crusting, inflammation and infection have been evident. In addition apomorphine was found

to be subject to rapid oxidation in solution. To overcome these problems, a nasal-powder approach was developed.

Objects of the Invention

5 The overriding objective of this invention is the development of a liquid intranasal formulation of rotigotine salts that is stable, safe and effective. Aspects of the desired stability include an acceptable oxidative stability and a good
10 temperature stability. Aspects of formulation safety include, inter alia, no detectable microbiological contamination while retaining the possibility to avoid potentially irritating preservatives such as ethanol or benzalkonium chloride, even though such preservatives can be added according to necessity.
15 However, in a preferred aspect of the present invention the intranasal formulation is free of any preservatives yet remains antibacterially active. Further aspects of safety include low irritation of the nasal mucosa and avoidance of nasal vestibulitis. Aspects of formulation efficacy include
20 the possibility of administering sufficient quantities of rotigotine to a human subject suffering from Parkinson's Disease to achieve (a) a rotigotine plasma level in the order of at least 100 pg/ml and (b) a measurable improvement of the symptoms of Parkinson's Disease of at least 2 units in the
25 Unified Parkinson's Disease Rating Scale (UPDRS) compared to a placebo treatment. In the context of this application, "placebo treatment" refers to a treatment with an intranasal composition of identical qualitative composition but where the active ingredient has been omitted.

30

Summary of the Invention

Surprisingly it has been found that the above objectives could be obtained with a liquid intranasal pharmaceutical
35 formulation comprising a pharmaceutically acceptable acid addition salt of rotigotine and α -cyclodextrin. The most preferred pharmaceutically acceptable acid addition salt of rotigotine is the hydrochloride. Further pharmaceutically

acceptable acid addition salts that could be used include the urotrate, tartrate, citrate, phosphate, sulphate and the methanesulfonate. Additional preferred aspects of intranasal formulations according to the present invention are given in the appending dependent claims and in the following detailed description.

Detailed Description of the Invention

According to preferred aspects of the present invention said liquid intranasal formulation further contains buffer salts, e.g. phosphates or acetates, and as such may be present as a buffered aqueous solution. In a preferred embodiment, the intranasal formulation contains phosphate buffered saline (PBS) as buffer system.

The intranasal formulation according to the present invention may preferably further contain a viscosity-enhancing substance. Glycerol and carboxymethylcellulose (CMC) are particularly useful as viscosity enhancers, but the present invention is not limited thereto. Glycerol is particularly preferred as it also has a soothing effect on the nasal mucosa. The viscosity of the intranasal formulations of the present invention should preferably be between 0.8 and 1.5 mm²/s, most preferably around 1.2 mm²/s. The viscosity can be determined by an Ubbelohde capillary viscosimeter with suspending ball-level for the determination of kinematic viscosity according to DIN 51562, part 1. Moreover, glycerol in the formulation surprisingly serves to increase the uptake of rotigotine through the nasal mucosa as was shown by in-vitro permeation assays with nasal mucosa from freshly slaughtered cattle.

The pH-value of the formulation of the present invention should preferably in the range of 4.5 to 6.5, more preferably around 5.8 ± 0.3. The pH value of 5.8 leads to an optimal drug uptake as was revealed by in-vitro permeation assays. Surprisingly, a higher pH value of 6.5 as well as a lower pH

value of 4.5 in the formulation resulted in a significantly lower rotigotine uptake through nasal mucosa tissue from freshly slaughtered cattle. The pH value of the intranasal formulation can be adjusted during or after its preparation
5 with a pharmaceutically acceptable acid or base. Most preferably, citric acid is used for this purpose.

In a preferred aspect of the present invention the intranasal formulation does not contain a further absorption enhancer,
10 preservative and/or antioxidant. While such agents are commonly used in many commercial intranasal preparations, the formulation of the present invention can do without them without sacrificing safety and efficacy, or even improve safety and efficacy by omitting such agents.

15 Nevertheless, according to a less preferred aspect of the invention, it is also possible that the intranasal formulation contains further absorption enhancers. Such enhancers can suitably be selected from surfactants and/or emulsifiers,
20 particularly non-ionic surfactants such as TWEEN 80® or cremophor RH40®. As an antioxidant, the formulation may contain e.g. ascorbates or sorbates. Known preservatives that may, but do not need to be used in the formulation include antimicrobial substances such benzalkonium chloride. It is one
25 of the particularly advantageous and surprising features of the formulation according to the present invention that such antimicrobial preservatives are not needed, thus in a further aspect the present invention relates to an intranasal formulation as defined above that is free of preservatives.
30 The absence of preservatives such as benzalkonium chloride provides an additional advantage because this agent shows a significant ciliary toxicity. Experiments conducted by the applicant show that even a formulation according to the invention that is free from preservatives shows no microbial
35 contamination and satisfies the standards for topical formulations according to Ph. Eur., 4 Ed.

α -Cyclodextrin is a particularly important component of the present invention. The inventors have discovered that, unexpectedly, α -cyclodextrin markedly increases the storage stability of the intranasal formulation, even when compared to β -cyclodextrin. Moreover, α -cyclodextrin seems to have a much better solubility-enhancing effect on rotigotine hydrochloride than β -cyclodextrin. The concentration of α -cyclodextrin in solution does not need to be higher than 0.5 g/ml and is preferably in the range of 0.001 - 0.1 g/ml, more preferably between 0.05 and 0.1 g/ml and most preferably 0.05 - 0.085 g/ml.

Cyclodextrins per se, among many other agents, have been proposed for nasal drug delivery before, see e.g. Merkus et al in Advanced Drug Delivery Reviews 36 (1999) 41-57. However, the review of Merkus does not specifically address rotigotine and, on the whole, rather seems to prefer β -cyclodextrins and particularly methylated β -cyclodextrins. The article further notes large interspecies differences and cautions against blindly transferring the results of rat studies to humans.

The intranasal formulation according to a preferred aspect of the present invention may contain 1 - 6 mg/ml rotigotine-HCl in an aqueous buffered solution. According to a further and independent aspect of the present invention, the intranasal formulation contains between 0.03 and 0.1 g/ml α -cyclodextrin in the solution.

Particularly preferred intranasal formulations according to the present invention consist of 2 - 5 mg/ml rotigotine-HCl, 0.05 - 0.1 g/ml α -cyclodextrin and 2.2 - 3 vol.% glycerol in an aqueous buffer, such as phosphate buffered saline (PBS).

Examples

The following examples are to illustrate the invention without limiting it. All parts and percentages are volume-based unless
5 indicated otherwise.

Example 1

10 The following intranasal formulation according to the present invention was prepared:

2.5 g/L	Rotigotine-HCl
85 g/L	α -Cyclodextrin
15 8 g/L	NaCl
0.2 g/L	KCl
1.44 g/L	$\text{Na}_2\text{HPO}_4 \times 2\text{H}_2\text{O}$
0.2 g/L	KH_2PO_4
31.2 g/L	Glycerol (87 % solution in water)
20 water to add up to final volume	
citric acid for pH adjustment	
pH of solution 5.8	

610 ml water was adjusted to pH 3 with citric acid and alpha-
25 cyclodextrin, glycerol and rotigotine hydrochloride were added to give a concentration of 85 mg/ml, 2.6 vol. % and 2.5 mg/ml respectively. Subsequently, 250 ml of 4xPBS buffer solution (having four times the concentration of standard PBS buffer solution, i.e. a concentration of 32 g/l NaCl, 0.8 g/l KCl,
30 5.76 g/l $\text{Na}_2\text{HPO}_4 \times 2 \text{H}_2\text{O}$ and 0.8 g/l KH_2PO_4 in water) was added, followed by drop wise addition of 1 M citric acid until a pH of 5.8 was reached. Water was used to fill up to a final volume of 1000 ml.

35 The obtained solution was filtered through 0.22 μm PES filter. The solution may be filled in suitable pharmaceutical containers, e.g. dark vials of 8 ml volume, and is ready for intranasal administration to mammals, including man.

Example 2

The (maximum) solubility of rotigotine-HCl in aqueous solution at room temperature (20 °C) can be significantly improved by the use of α -cyclodextrin (α -CD) while there is no significant increase in rotigotine solubility when β -cyclodextrin is used. For cyclodextrin concentrations which are close to the maximum solubility of each of the two CD types, 5.03 mg/mL rotigotine-HCl could be dissolved in an 0.1 g/mL α -CD solution but only 1.57 mg/mL could be dissolved in a 0.015 g/mL β -CD solution.

The concentration was determined by isocratic HPLC analysis. HPLC column LiChroCART 75x4 mm, Superspher 60 RP-select B 5 μ m (Merck), column temperature: 30°C, mobile phase: water/acetonitrile/methane sulfonic acid (65/35/0.05 v/v/v), flow rate: 2 mL/min, injection volume: 50 μ L, detection at 220 nm, retention time approx. 1.5 min. The concentration was determined by use of an external reference solution with known concentration.

The results are shown in the following table 1:

Table 1

CD-Concentration [g/mL]	Rotigotine hydrochloride [mg/mL]		Rotigotine base [mg/mL]	
	α -CD	β -CD	α -CD	β -CD
0	1.05	1.05	0.15	0.15
0.005	n.d.	1.34	n.d.	0.21
0.01	1.39	1.40	0.19	0.22
0.015	n.d.	1.57	n.d.	0.22
0.05	3.0	*	0.34	*
0.1	5.03	*	0.57	*

n. d. = no data available

* = exceeds maximum β -CD solubility in the solution tested

Very surprisingly, it was shown that the solubility of rotigotine hydrochloride is increased five-fold by adding 0.1 g/ml α -cyclodextrin (α -CD) whereas the maximum solubility-enhancing effect of β -CD was only very moderate (factor 1.6). Rotigotine base is practically insoluble both in aqueous solution and in aqueous solutions containing α - or β -cyclodextrin. The full beneficial effects of the present invention can therefore only be obtained by using α -cyclodextrin. This effect was surprising and unpredictable on the basis of the available data on rotigotine.

Example 3

To evaluate the storage stability of potential nasal formulations of rotigotine hydrochloride the following formulations were prepared:

Formulation sample A (comparative example):

2.5 g/L	Rotigotine-HCl
0.5 % (v/v)	Tween 80
8 g/L	NaCl
0.2 g/L	KCl
1.44 g/L	$\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$
0.2 g/L	KH_2PO_4
water to add up to final volume	
citric acid for pH adjustment, pH 5.8	

470 ml water were adjusted to pH 3 with citric acid and Tween 80 and rotigotine hydrochloride were added to give a concentration of 0.5 vol. % and 2.5 mg/ml respectively. Subsequently, 200 ml of 4x PBS buffer solution was added, followed by drop wise addition of 1 M citric acid until a pH of 5.8 was reached. Water was used to fill up to a final volume of 800 ml.

Formulation sample B (inventive formulation):

2.5 g/L Rotigotine-HCl
5 85 g/L α -Cyclodextrin
8 g/L NaCl
0.2 g/L KCl
1.44 g/L $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$
0.2 g/L KH_2PO_4
10 water to add up to final volume
citric acid for pH adjustment, pH 5.8

470 ml water was adjusted to pH 3 with citric acid and α -cyclodextrin and rotigotine hydrochloride were added to give a
15 concentration of 85 mg/ml and 2.5 mg/ml respectively.
Subsequently, 200 ml of 4xPBS buffer solution were added,
followed by drop wise addition of 1 M citric acid until a pH
of 5.8 was reached. Water was used to fill up to a final
volume of 800 ml.

20

The stability was determined by measuring the concentration of rotigotine over time using gradient HPLC analysis.
HPLC column: Licrospher 100 CN, 5 μm , 125 x 4.6 mm (Bidhoff),
pre column filter: 2 μm , mobile phase A: water/methane
25 sulfonic acid (1000/0.5 (v/v)), mobile phase B:
acetonitrile/methane sulfonic acid 1000/0.5 (v/v)), flow rate
1.0 mL/min, profile of the gradient: 0 min 95 % A / 5 % B; 2
min 95 % A / 5 % B; 35 min 40 % A / 60 % B; 38 min 40 % A / 60
% B; 39 min 95 % A / 5 % B; initial pressure approx. 90 bar,
30 injection volume 80 μl , detection at 220 nm and 272 nm,
retention time approx. 18 min. All peaks in the chromatogram
with an area > 0.05 % were integrated up to a retention time
of 35 minutes to calculate the purity of the drug substance.
The relative purity is used to calculate the degradation of
35 Rotigotine hydrochloride. The results are shown in Table 2.

Table 2:

	Sample A (Tween 80, without α -CD)		Sample B (with α -CD)	
	220 nm	272 nm	220 nm	272 nm
Rotigotine degradation * 6 weeks 60 °C	-5,6	-11,1	-1,0	-5,6
Rotigotine degradation * 1 year 40 °C	-6,0	-9,1	-0,4	-2,0
Rotigotine degradation * 1 year 25 °C	-2,6	-3,1	± 0.0	+0.2**

* These values reflect the loss in rotigotine absorption
5 between the start values and the actual test points at the
given conditions.

** The apparent increase in purity can be explained by the
measurement accuracy of the analytical method. The result
10 should be interpreted as no significant change in purity
relative to the starting value at t=0.

It is readily apparent from Table 2 that α -cyclodextrin
(sample B) markedly increased stability of rotigotine
15 hydrochloride as compared to the Tween 80 formulation (sample
A). The stabilizing effect of α -cyclodextrin becomes also
apparent from a comparative test in an aqueous rotigotine
solution. Following storage at 60°C for 8 weeks, a rotigotine
solution of 1.6 mg/ml with α -cyclodextrin showed a decrease in
20 the rotigotine concentration of -0.07 mg/ml, whilst a solution
of 1.9 mg/ml of rotigotine without α -cyclodextrin showed a
decrease of -0.22 mg/ml.

Example 4

	2.5 g/L	Rotigotine-HCl
	50 g/L	α -Cyclodextrin
5	4 g/L	NaCl
	0.1 g/L	KCl
	0.72 g/L	$\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$
	0.1 g/L	KH_2PO_4
	31.2 g/L	Glycerol (87% solution in water)

10

470 ml water was adjusted to pH 3 with citric acid and α -cyclodextrin, glycerol and rotigotine hydrochloride were added to give a concentration of 50 mg/ml and 2.5 mg/ml, respectively.

15

Subsequently, 200 ml of 2xPBS buffer solution were added, followed by drop wise addition of 1 M citric acid until a pH of 5.8 was reached. Water was used to fill up to a final volume of 800 ml.

20

Claims

- 5 1. Liquid intranasal pharmaceutical formulation comprising a
pharmaceutically acceptable acid addition salt of rotigotine
and α -cyclodextrin.
- 10 2. Intranasal formulation according to claim 1 characterised
in that it further contains a buffer system.
3. Intranasal formulation according to claim 2 characterised
in that the buffer system is phosphate buffered saline (PBS).
- 15 4. Intranasal formulation according to any of the preceding
claims characterised in that it further contains a viscosity-
enhancing substance so as to give a viscosity of 0.5 -
1.5 mm²/s.
- 20 5. Intranasal formulation according to claim 4 characterised
in that the viscosity-enhancing substance is glycerol.
6. Intranasal formulation according to any of the preceding
claims characterised in that it has a pH-value in the range of
25 5 - 6.5.
7. Intranasal formulation according to any of the preceding
claims characterised in that it further contains a
pharmaceutically acceptable acid for the adjustment of the pH-
30 value.
8. Intranasal formulation according to claim 7 characterised
in that the pharmaceutically acceptable acid is citric acid.
- 35 9. Intranasal formulation according to any of the preceding
claims characterised in that the formulation does not contain
a solubility enhancer.

10. Intranasal formulation according to any of the preceding claims characterised in that it does not contain any preservative.
- 5 11. Intranasal formulation according to any of the preceding claims characterised in that it does not contain any antioxidants.
- 10 12. Intranasal formulation according to any of the preceding claims characterised in that it further contains an absorption enhancer selected from non-ionic surfactants.
- 15 13. Intranasal formulation according to claim 12 characterised in that the absorption enhancer is TWEEN 80 or cremophor RH40.
14. Intranasal formulation according to any of the preceding claims characterised in that the pharmaceutically acceptable acid addition salt of rotigotine is rotigotine hydrochloride.
- 20 15. Intranasal formulation according to any of the preceding claims characterised in that it contains 1 - 6 mg/ml rotigotine-HCL in an aqueous buffered solution.
- 25 16. Intranasal formulation according to any of the preceding claims characterised in that the formulation contains between 0.03 and 0.1 g/ml α -cyclodextrin in the solution.
- 30 17. Intranasal formulation according to any of the preceding claims characterised in that it consists of 2 - 5 mg/ml rotigotine-HCl, 0.05 - 0.1 g/ml α -cyclodextrin and 2.2 - 3 % glycerol in phosphate buffered saline (PBS).
- 35 18. Intranasal formulation according to claim 17 characterised in that it further contains citric acid to adjust the pH-value between 5 and 6.5.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/014626

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/381

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 756 483 A (MERKUS FRANCISCUS W H M) 26 May 1998 (1998-05-26) column 4, lines 26-41	1-18
P, A	MUCKE H A M: "ROTIGOTINE SCHWARZ PHARMA" IDRUGS, CURRENT DRUGS LTD, GB, vol. 6, no. 9, 2003, pages 894-899, XP001157133 ISSN: 1369-7056 the whole document	1-18
A	US 2003/166709 A1 (KREIN CLIFF ET AL) 4 September 2003 (2003-09-04) paragraph '0103!; claim 1	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

8 document member of the same patent family

Date of the actual completion of the international search

16 February 2005

Date of mailing of the international search report

04/03/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Cattell, James

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/014626

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5756483	A	26-05-1998	BE 1006870 A6	10-01-1995
			BE 1006871 A6	10-01-1995
			BE 1006872 A6	10-01-1995
			AT 241984 T	15-06-2003
			AU 6428894 A	24-10-1994
			DE 69432789 D1	10-07-2003
			DE 69432789 T2	04-12-2003
			DK 689438 T3	29-09-2003
			WO 9422445 A2	13-10-1994
			EP 0689438 A1	03-01-1996
			EP 0865789 A2	23-09-1998
			ES 2194867 T3	01-12-2003
			JP 8508472 T	10-09-1996
			PT 689438 T	31-10-2003
			US 5942251 A	24-08-1999
US 2003166709	A1	04-09-2003	DE 10041479 A1	14-03-2002
			AU 8982001 A	04-03-2002
			CA 2420061 A1	20-02-2003
			WO 0215903 A2	28-02-2002
			EP 1313467 A2	28-05-2003
			JP 2004520269 T	08-07-2004